

Introduction to the Session: Combinations of Molecularly Targeted Agents in Cancer

Larry Norton, MD

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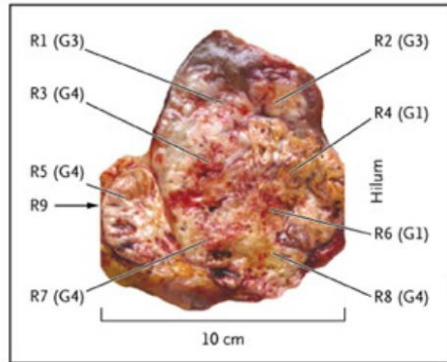
Neal Rosen, MD, PhD

Memorial Sloan Kettering Cancer Center

October 21, 2014



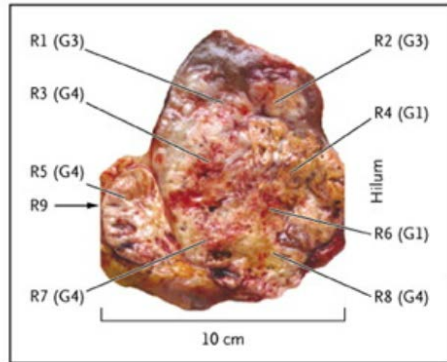
Combinations are rational



Intratumoral Heterogeneity

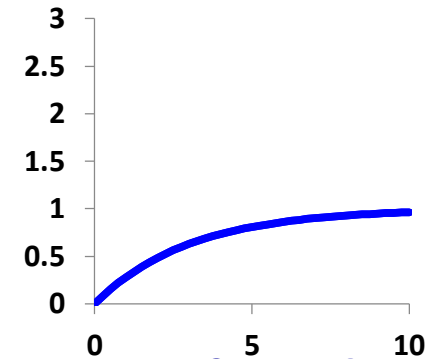
Gerlinger...Swanton, NEJM, 2012

Combinations are rational



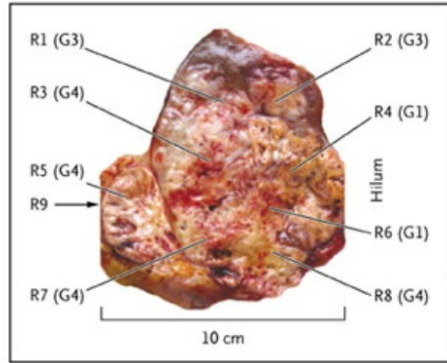
Intratumoral Heterogeneity

Gerlinger...Swanton, NEJM, 2012



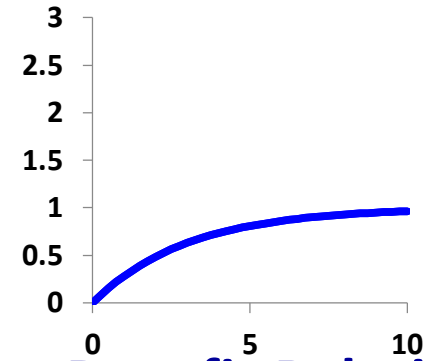
Dose-Benefit Relationships

Combinations are rational

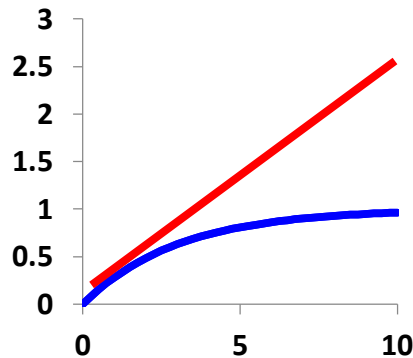


Intratumoral Heterogeneity

Gerlinger...Swanton, NEJM, 2012



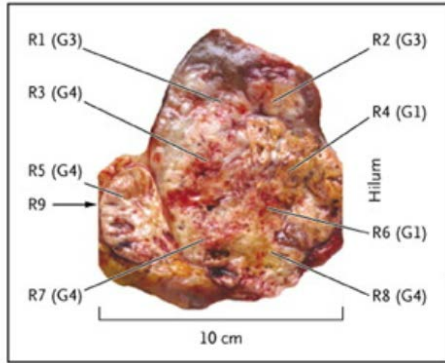
Dose-Benefit Relationships



Dose-Toxicity Relationships

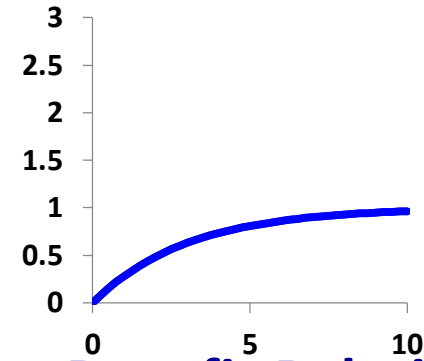


Combinations are rational

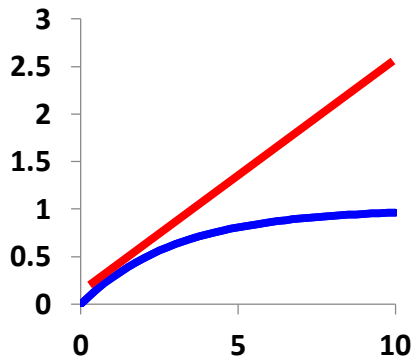


Intratumoral Heterogeneity

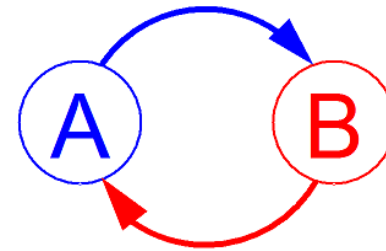
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Dose-Benefit Relationships



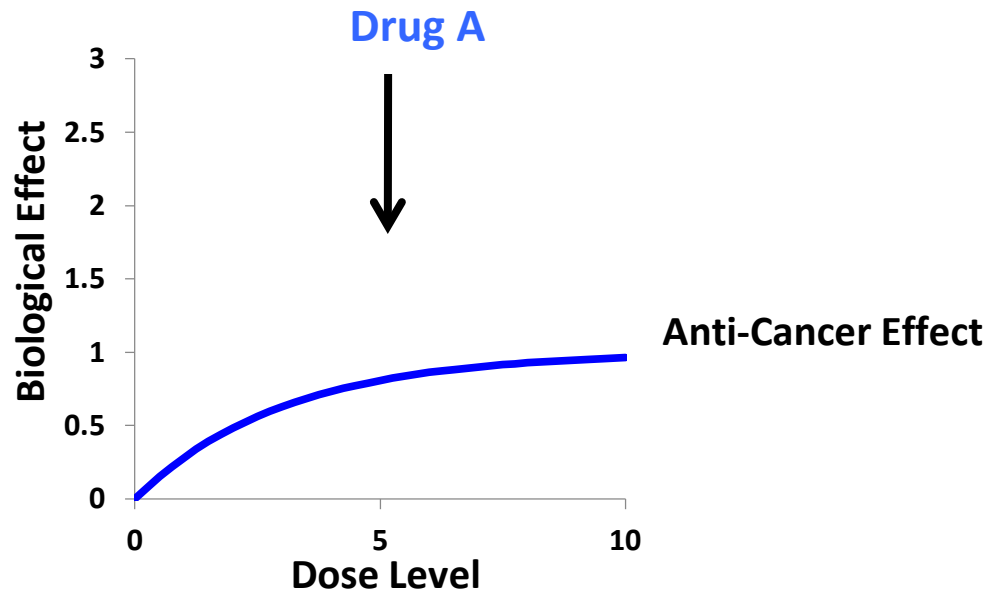
Dose-Toxicity Relationships



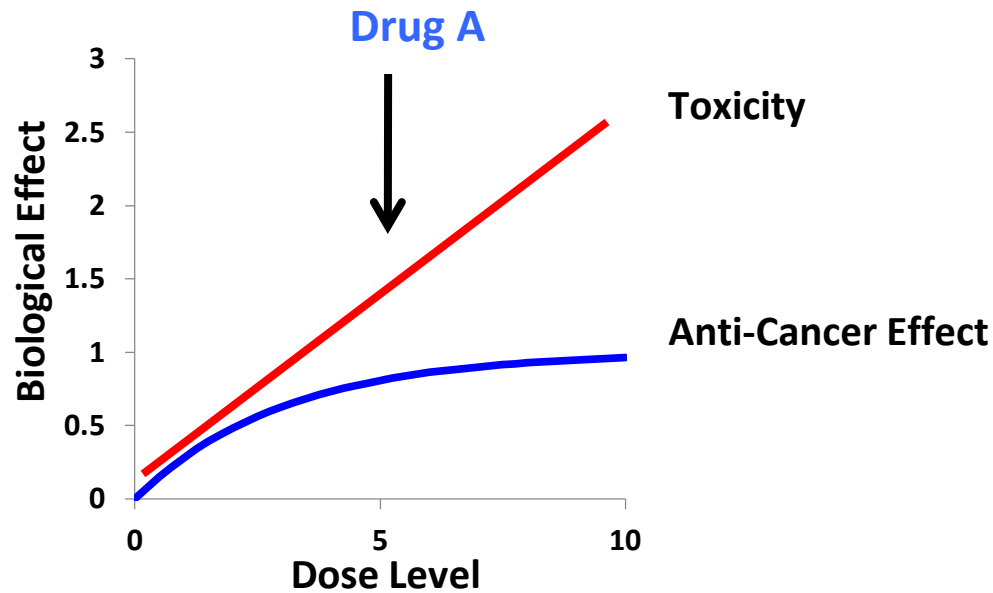
Implications of Feedback



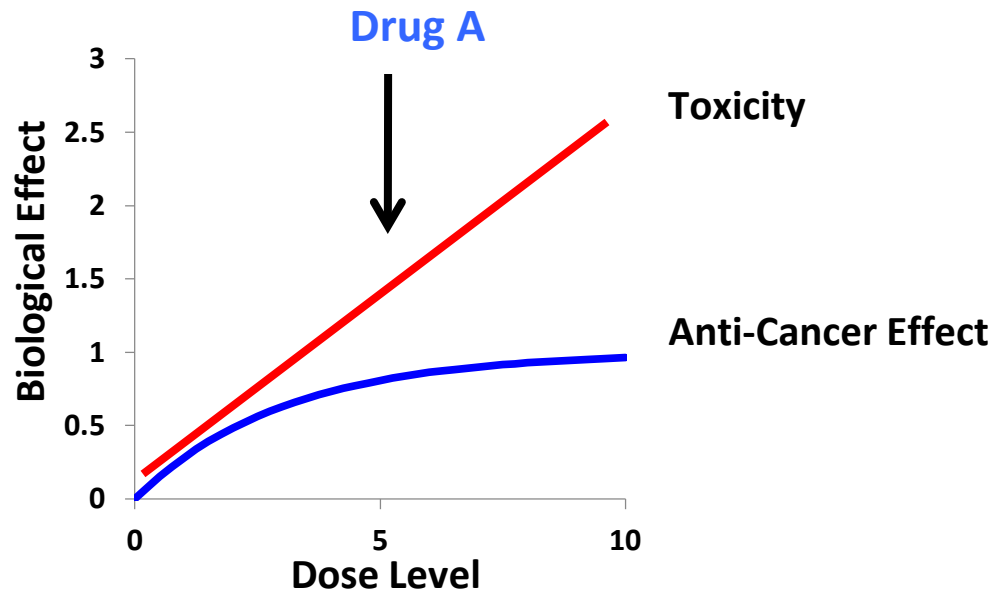
Efficacy (benefit) may not increase linearly with dose level



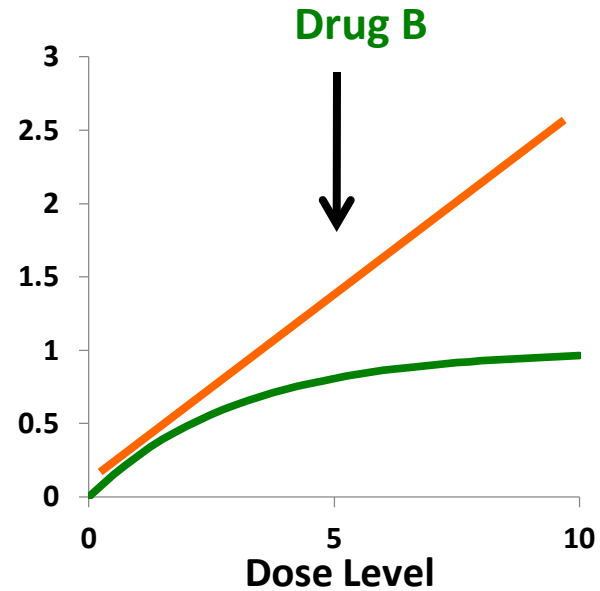
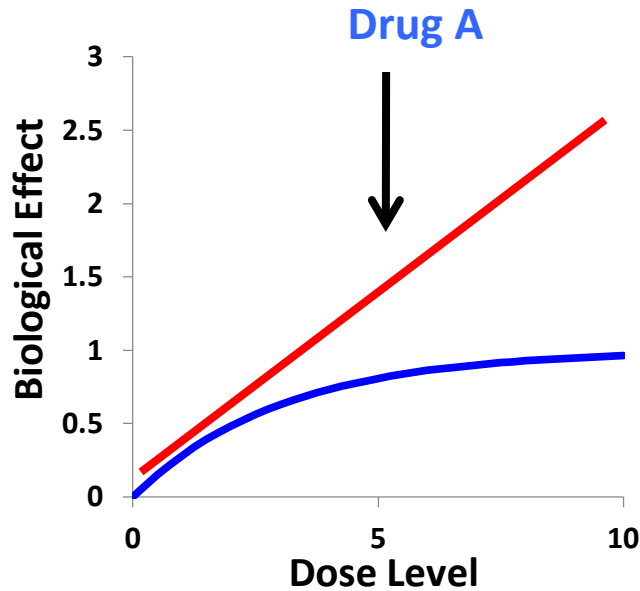
Toxicity, however, may increase linearly with dose level



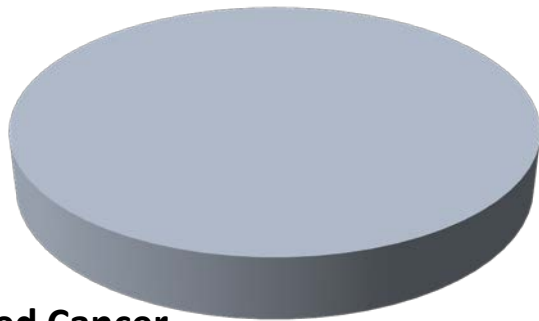
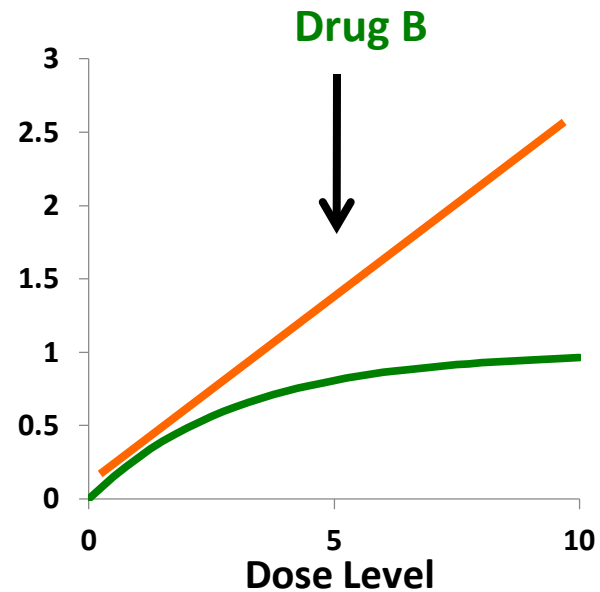
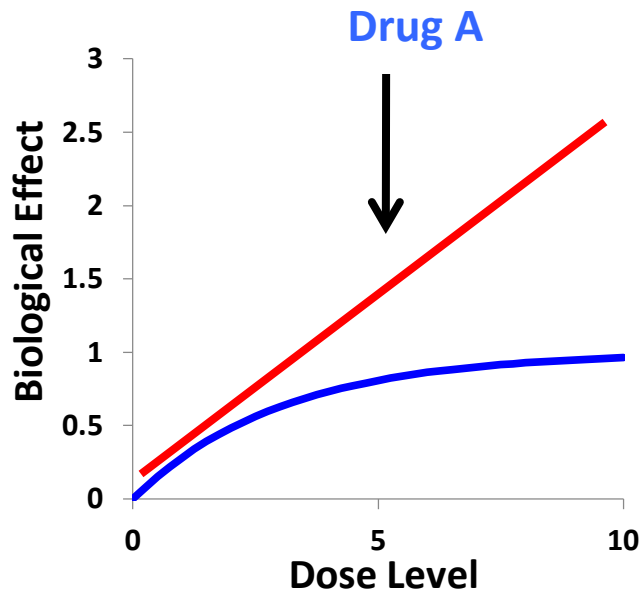
Hence, increasing the dose level of drug A alone would increase toxicity while not increasing efficacy



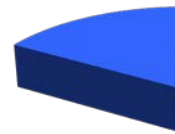
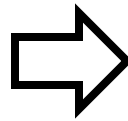
But A plus B could increase efficacy while not increasing non-overlapping toxicity



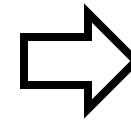
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Untreated Cancer



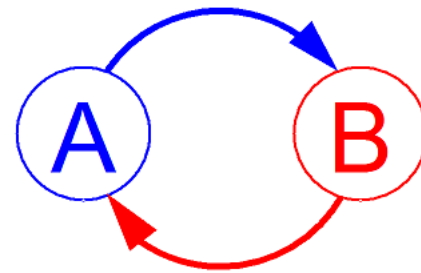
Part Surviving Drug A



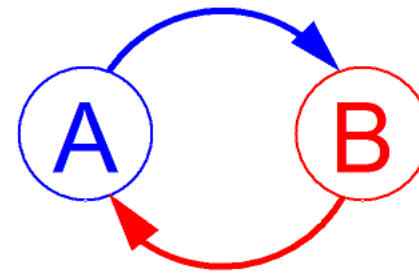
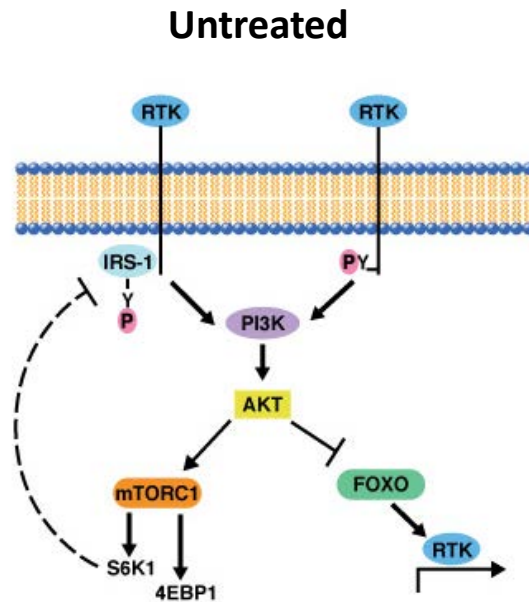
Part Surviving Drugs A + B



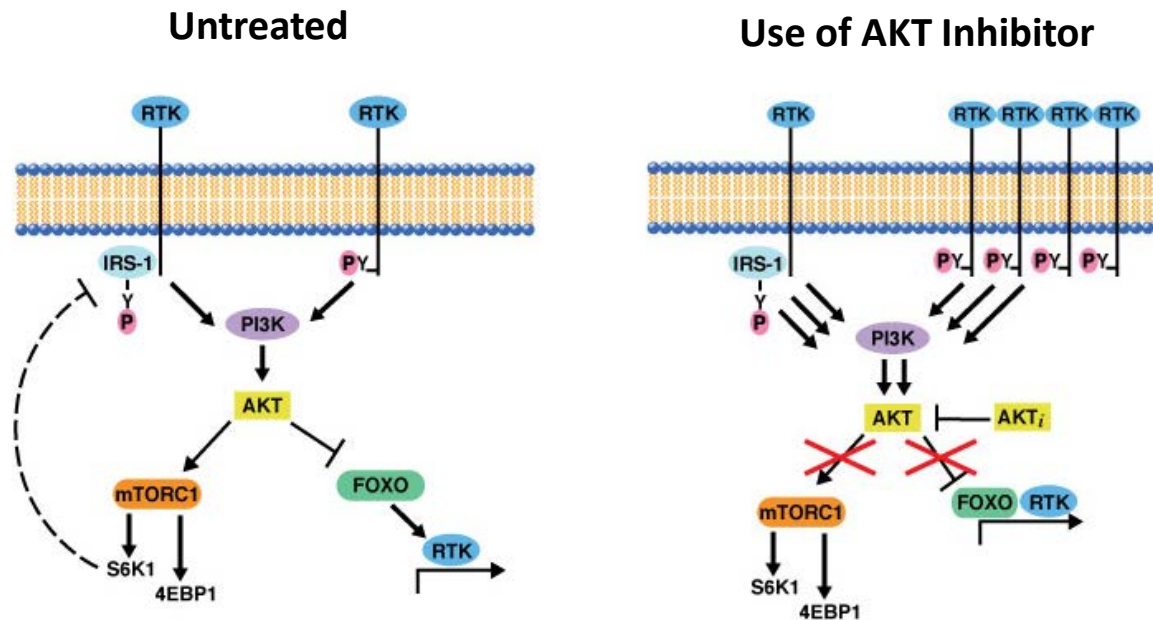
Feedback:



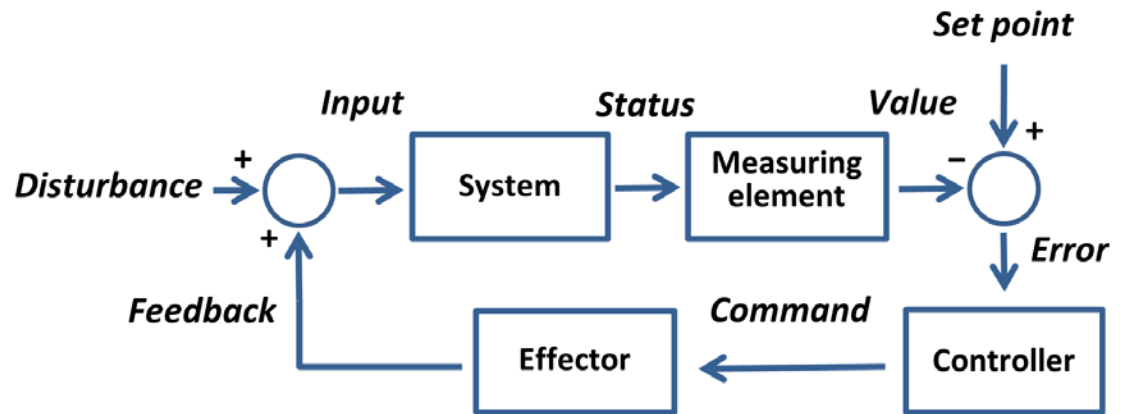
Feedback: In the untreated situation AKT/mTOR activity is regulated by feedback



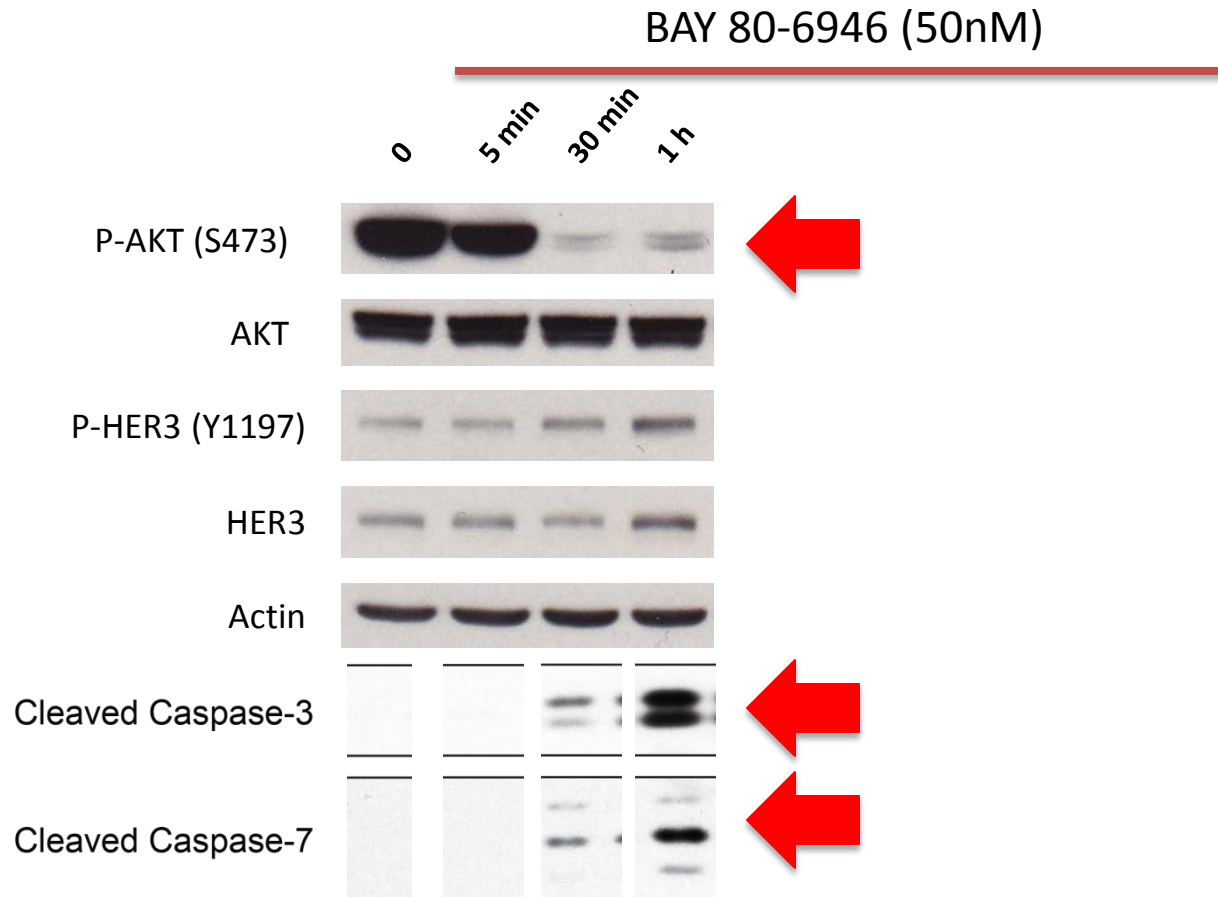
Feedback: Inhibition of AKT/mTOR reduces normal feedback inhibition and thereby activates RTK/PI3K signaling



However, feedback is a complex process, and therefore is not instantaneous



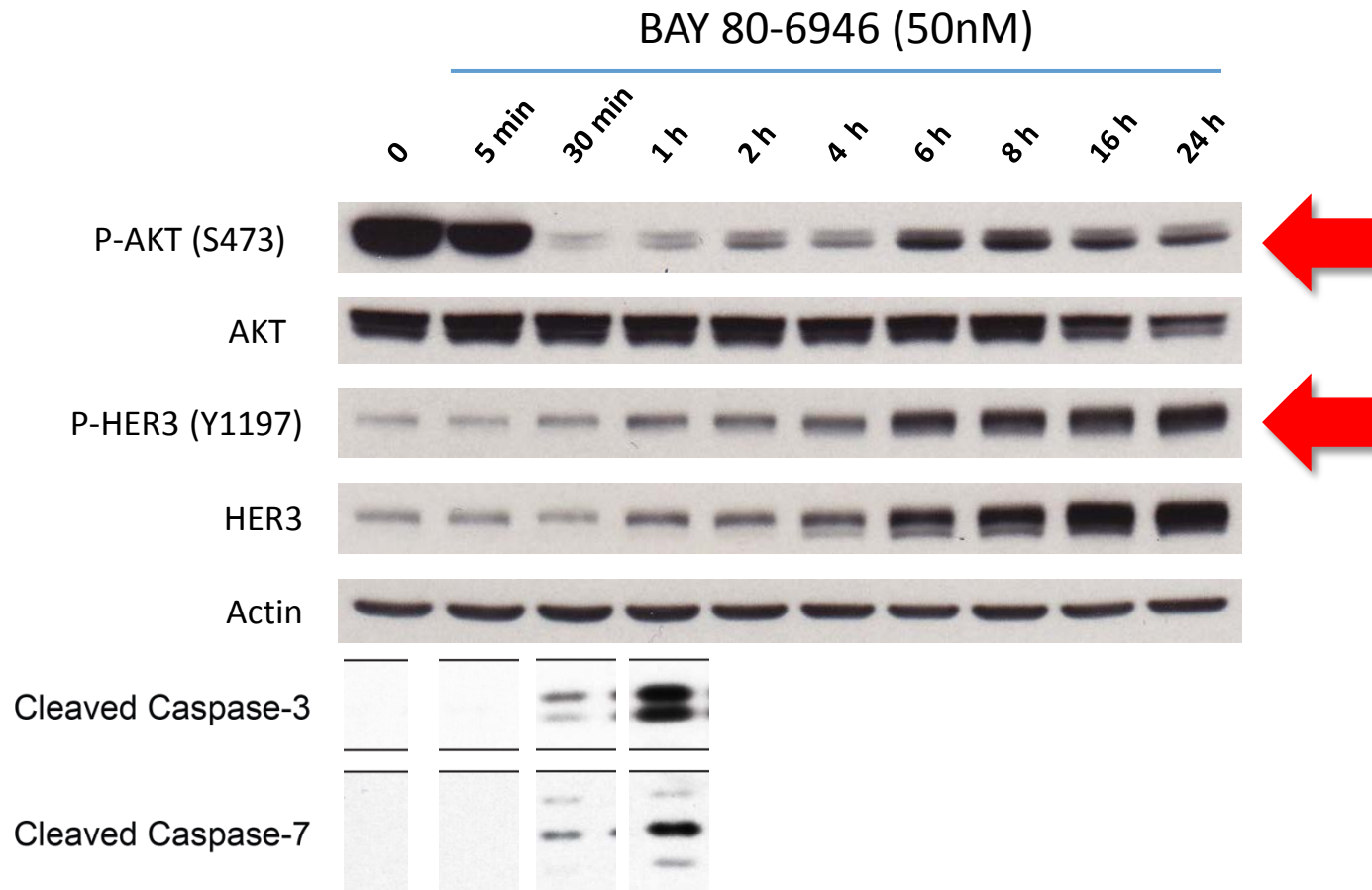
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Will M, Chandarlapaty S, Rosen N *et al.* (In part: Cancer Discovery, 2014)



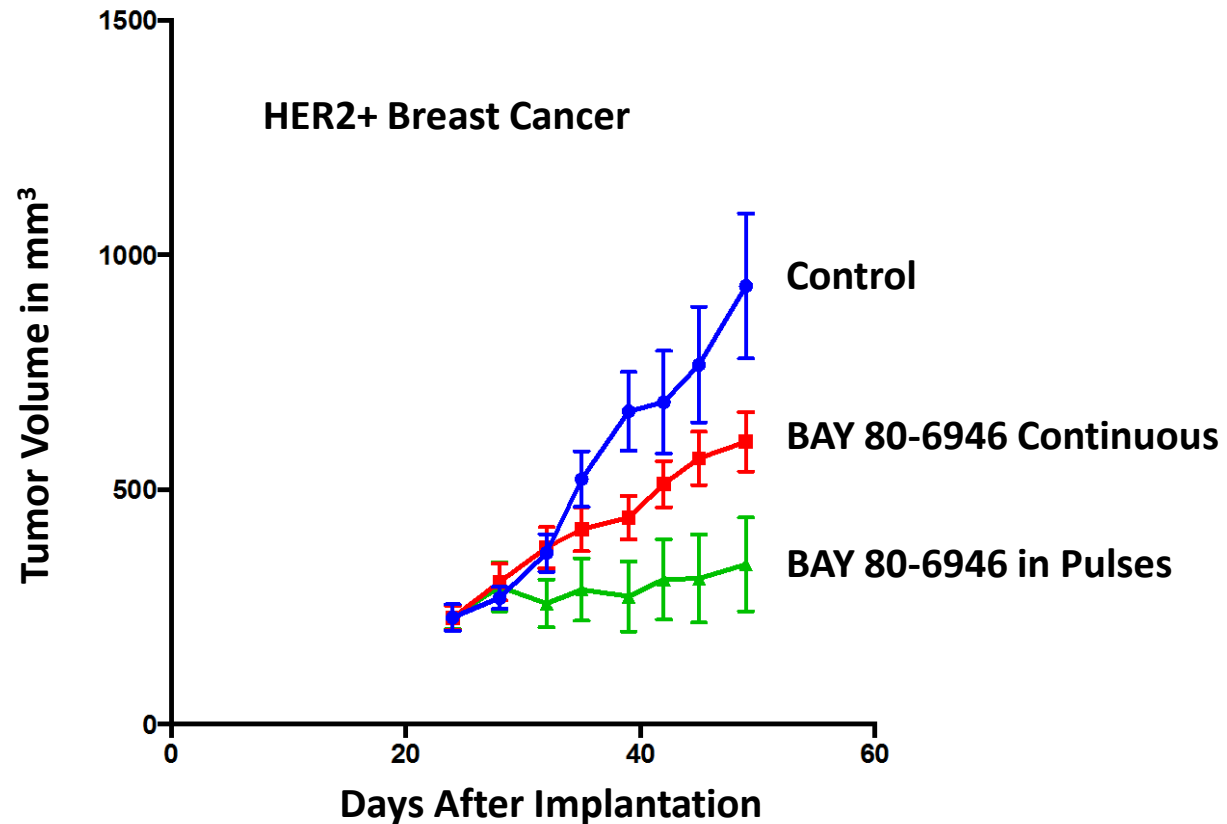
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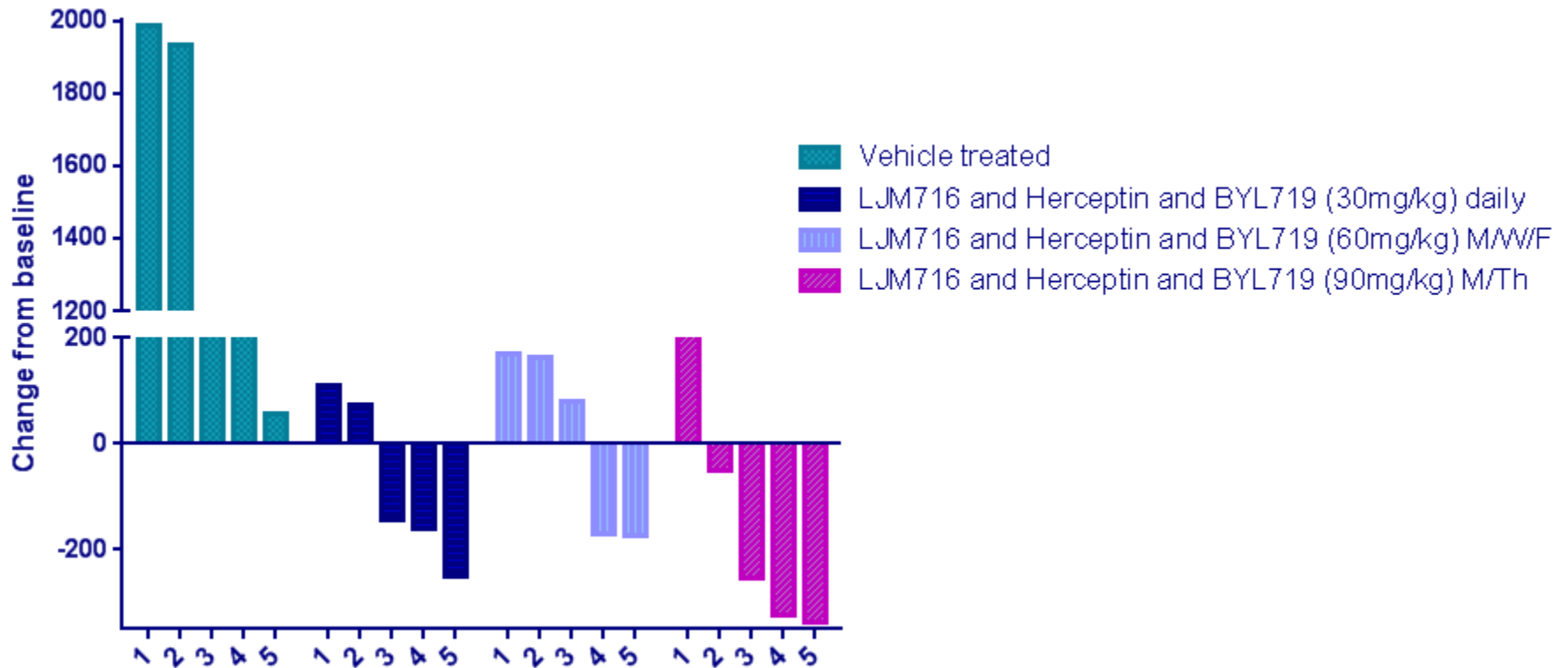
Hence, intermittent exposure can be more effective than continuous exposure



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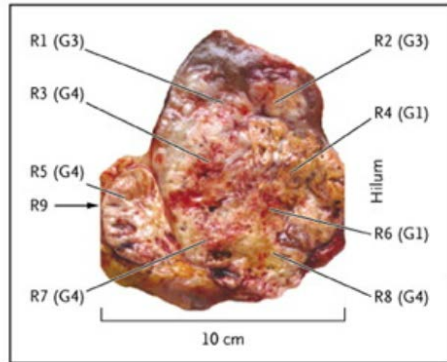
Moreover, intermittent exposure can be augmented by HER2 and HER3 inhibition



Gala K, Chandarlapaty S, Rosen N *et al.*, 2014

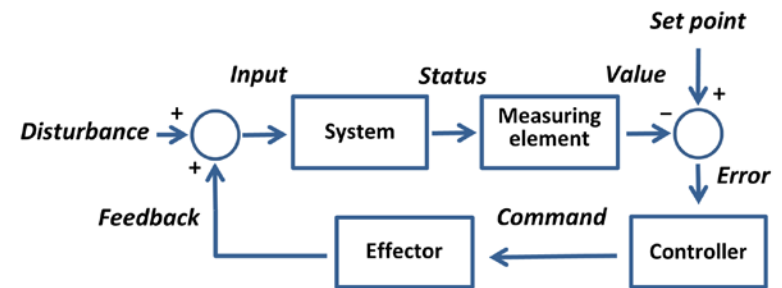
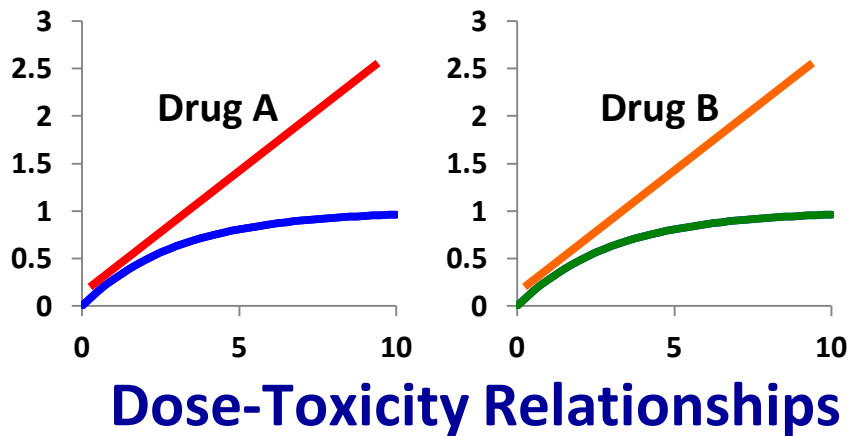
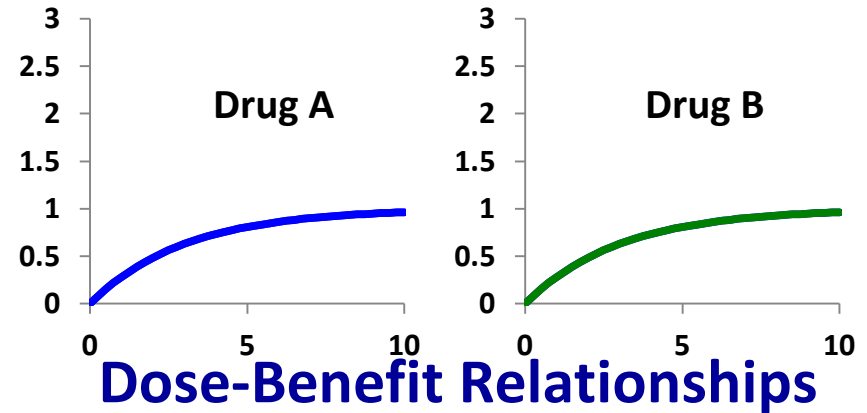


Conclusion: Combinations are rational and may be essential



Intratumoral Heterogeneity

Gerlinger...Swanton, NEJM, 2012



Implications of Feedback



Thank You!

